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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/373,333 | 08/12/1999 | VENKITESWARAN SUBRAMANIAN | 0113.410US | 2490 |

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| EXAMINER | |
|---|---|
| JOHANNSEN, DIANA B | |

| ART UNIT | PAPER NUMBER |
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| 1634 | |

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27

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/373,333 | Applicant(s) SUBRAMANIAN ET AL. | |
|---|---|---|---|
| | Examiner Diana Johannsen | Art Unit 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *4,6-8,11,14-16,18-20,22-24,28,30,32-37 and 61-67* is/are pending in the application.

4a) Of the above claim(s) *38-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6-8,11,14-16,18-20,22-24,28,30,32-37 and 61-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

## DETAILED ACTION

### *Continued Prosecution Application*

1. The request filed on January 31, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/373,333 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1-3, 5, 9-10, 12-13, 17, 21, 25-27, 29 and 31 have been canceled, claims 4, 6-8, 14, 19-20, 22-24, 28, 30, 32-35, 37, and 61 have been amended, claims 62-67 have been added, and claims 38-60 have been withdrawn from consideration. Claims 4, 6-8, 11, 14-16, 18-20, 22-24, 28, 30, 32-37, and 61-67 are now under consideration. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims.

### *Election/Restriction*

3. Claims 38-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 16.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 4, 6-8, 11, 14-16, 18-20, 22-24, 28, 30, 32-37, and 61-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 6-8, 11, 14-16, 18-20, 22-24, 28, 30, 32-37, and 61-67 are indefinite for failing to recite a final process step that clearly relates back to the claim preamble. The claims are drawn to a method "of obtaining a recombinant herbicide tolerant nucleic acid that encodes an herbicide tolerance polypeptide", yet recites a final process step of screening a library "to detect a recombinant herbicide tolerance nucleic acid that encodes an herbicide tolerance polypeptide." The claims do not set forth how screening to detect a nucleic acid results in "obtaining" a nucleic acid, and it is unclear as to whether the claims are intended to require detection of a nucleic acid or "obtaining" a nucleic acid. Clarification is required.

Claims 65-66 are indefinite because it is unclear as to how the claims are intended to further limit claim 4. Claim 65 is drawn to a method that "further comprises" steps (a) and (b). However, the claim does not make clear whether these steps are intended further limit previously recited steps (a) and (b), respectively, or whether the method is to further comprise an additional step (a) and an additional step (b). Clarification is required.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 4, 6-7, 11, 14-16, 18-20, 23-24, 28, 30, 32-33, 35-37, and 61-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla et al (U.S. Patent No. 5,521,077 [5/1996]) in view of Subramanian et al (J. Industrial Microbiol. & Biotechnol. 19:344-349 [1997]) and Sack et al (J. Structural Biology 117:73-76 [1996]).

Khosla et al teach a method termed "recombination-enhanced mutagenesis" in which "large populations of protein variants" are produced *in vivo* by recombination of multiple sets of allelic variants (see entire reference, especially, e.g., col 1 lines 8-14, col 2, lines 5-64). Khosla et al disclose methods in which steps of recombining "variant forms" *in vivo* to produce a recombinant library are followed by a step of screening recombinants for proteins having desired activities (see, e.g., col 2, lines 57-61; col 4, lines 51-58; col 6, line 64-col 7, line 10; Fig. 1). Khosla et al state that recombinants generated by their methods can be "subjected to selection or screening by any appropriate method depending on the sought after characteristic or property of the protein of interest, for example, enzymatic or other biological activity, binding to a receptor molecule, inhibition of the binding of another receptor ligand, or the like" (col 7, lines 5-10). However, Khosla et al do not teach employing in their methods a gene

encoding an UDP-N-acetylglucosamine enolpyruvyltransferase, or teach methods in which a "recombinant herbicide tolerance nucleic acid" whose expression renders cells herbicide tolerant is detected or obtained. Subramanian et al disclose that herbicide tolerance is desirable in crops, and disclose that genes conferring herbicide tolerance, including "herbicide tolerance" genes obtained from bacteria, may be incorporated into plants (see entire reference, especially p. 344-345, Table 1). Subramanian et al further disclose that it is beneficial for plants to contain multiple herbicide-metabolizing enzymes (p. 344). Subramanian et al also teach methods of screening for new enzymes that confer herbicide tolerance (see, e.g., p. 347), and teach that the identification of novel genes conferring tolerance is beneficial because it provides "more options" for use in transgenic crops (p. 344). Sack et al disclose that UDP-N-acetylglucosamine enolpyruvyltransferase (EPT) shares structural and functional properties with EPSP synthase (p. 73-74). Sack et al further disclose that, unlike EPSP synthase, EPT is tolerant of the herbicide glyphosate (see p. 74). In view of the teachings of Subramanian et al and Sack et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the "recombination-enhanced mutagenesis" method of Khosla et al so as to have recombined variant forms of nucleic acids encoding EPT and to have screened the resultant recombinant libraries for herbicide tolerance, including glyphosate tolerance and novel mechanisms of glyphosate tolerance. Subramanian et al clearly disclose that the property of herbicide tolerance constitutes, using the language of Khosla et al set forth above, a "sought after characteristic or property". Further, the teachings of

Subramanian et al reveal a need for multiple, novel, variant genes that can be used to confer tolerance to crops, and Khosla et al disclose that their "recombination-enhanced mutagenesis" method permits efficient preparation of large, high quality populations of recombinants for screening (see, e.g., col 2, lines 5-61). Finally, Sack et al disclose that EPT is glyphosate tolerant, providing motivation to one of skill in the art to detect and obtain novel variants of EPT that would impart glyphosate tolerance in various settings, including, e.g., pathways functioning in plants. Accordingly, an ordinary artisan would have been motivated to have modified the method of Khosla et al for the advantage of rapidly and efficiently detecting and obtaining novel EPT variants conferring herbicide tolerance in a cell.

With respect to claim 6, Khosla et al teach the use of allelic variants of "parental" nucleic acids in their methods (see, e.g., col 2, lines 33-38). With respect to claim 7, Khosla et al disclose the preparation of a plurality of variants that would be homologous to the "parental nucleic acid" (col 5, lines 11-44). With respect to claim 14, the libraries taught by Khosla et al are present in a "population of cells", as required by the claims. With respect to claims 15-16, Subramanian et al disclose a variety of methods of screening for herbicide tolerance (see, e.g., Fig. 2 and Fig. 3). With respect to claims 18-20, Subramanian et al teach screening by assaying for growth in media comprising the herbicide of interest (p. 347). With respect to claim 23, Subramanian et al disclose that it is beneficial for plants to contain multiple herbicide-metabolizing enzymes (p. 344), and thereby provide motivation to screen for multiple herbicide tolerance activities. With respect to claim 24, the recombining step taught by Khosla et al requires a

"plurality of cells"(see, e.g., col 2, lines 30-64). With respect to claim 28, Khosla et al disclose that repetition of their methods may be used to generate additional, distinct recombinant molecules (see, e.g., col 7, lines 11-23). With respect to claim 30, Khosla et al teach performance of their methods using bacterial cells (see, e.g., claim 16). With respect to claims 32-33, Subramanian et al discloses that herbicide tolerance genes can be transduced into plants as a means of improving crops, and disclose that herbicide tolerance proteins should function "in a plant environment", thereby providing motivation to screen transgenic plants for herbicide tolerance (p. 344). With respect to claims 35-37, it is a property of the recombinant libraries prepared by the methods of Khosla et al in view of Subramanian et al and Sack et al that they would constitute recombinant libraries and comprise recombinant "herbicide tolerance" nucleic acids. With respect to claim 61, Khosla et al disclose isolating/recovering molecules that encode a polypeptide with an activity of interest (see, e.g., col 4, lines 35-43). With respect to claims 62-64, it is noted that it is a property of the EPT nucleic acid taught by Sack et al at page 74, left column, that it is a bacterial *MurA* gene corresponding to GenBank Accession No. Z11835 (see discussion of other prior art below, under the heading "Conclusion"). With respect to claims 65-67, it is further noted that Sack et al disclose that EPT and EPSP synthase share sequence similarity and have a common function in catalyzing the transfer of an enolpyruvyl moiety of PEP to a substrate (p. 73). Sack et al further disclose that while EPSP synthase is glyphosate sensitive, EPT is not. Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have provided EPSP synthase genes or any segments thereof

(including segments "derived from" the SP3 binding region) in the method of Khosla et al in view of Subramanian et al and Sack et al, and to have recombined those genes or segments with EPT genes or segments as part of the practice of the method. An ordinary artisan would have been motivated to have made such a modification for the advantage of obtaining additional recombinant molecules encoding proteins capable of imparting herbicide tolerance in various settings, e.g., novel recombinants of the similar proteins EPT and EPSP synthase that would provide glyphosate resistance in different organisms (e.g., particular plants).

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla et al in view of Subramanian et al and Sack et al as applied to claims 4, 6-7, 11, 14-16, 18-20, 23-24, 28, 30, 32-33, 35-37, and 61-67, above, and further in view of Krebber et al (U.S. Patent No. 5,514,548 [5/1996]).

While Khosla et al teaches that mutagenesis of nucleic acids may be "accomplished by several different techniques known in the art" (col 5, lines 27-44), the combined references of Khosla et al, Subramanian et al and Sack et al do not teach or suggest producing variant forms of a parental nucleic acid by error-prone transcription or by replication in a mutator strain, as required by the instant claim. Krebber et al disclose that mutagenesis may be performed by a variety of methods, and specifically teach that propagation in mutator strains may be used to perform mutagenesis and results in "increased mutation rates". In view of the teachings of Krebber et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Khosla et al in view of Subramanian et and

Sack et al so as to have performed mutagenesis of parental genes by propagating those nucleic acids in a mutator strain. First, as Khosla et al suggest that a variety of mutagenesis methods may be employed successfully in their methods, an ordinary artisan would have been motivated to have employed in the method of Khosla et al in view of Subramanian et al and Sack et al any step that could conveniently be performed to accomplish mutagenesis, including propagation in a mutator strain (i.e., one would have been motivated to have selected this method in instances in which mutator cell lines were readily available, for the advantage of convenience). Additionally, as Krebber et al teaches that propagation in mutator cell lines results in "increased mutation rates", an ordinary artisan would have been further motivated to have employed this method for the advantage of rapidly generating populations of allelic variants.

10. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla et al in view of Subramanian et al and Sack et al as applied to claims 4, 6-7, 11, 14-16, 18-20, 23-24, 28, 30, 32-33, 35-37, and 61-67, above, and further in view of Padgett et al (Herbicide-Resistant Crops, Duke, S.O., ed., CRC Lewis Publishers, Boca Raton, pp. 53-84 [1996]).

The combined references of Khosla et al, Subramanian et al and Sack et al do not teach or suggest the use of AroA- bacteria. Padgette et al teach that mechanisms of glyphosate tolerance include overproduction of EPSPS and "introduction of an EPSPS with decreased affinity for glyphosate" (p. 56). Padgette et al further teach that AroA- bacteria lack EPSPS activity, thereby disclosing to one of skill in the art that such

bacteria could not possess a native EPSPS that might confer glyphosate tolerance (see, e.g., p. 60). In view of the teachings of Padgette et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Khosla et al in view of Subramanian et al and Sack et al so as to have employed AroA- bacteria in screening for nucleic acids that possess EPSPS activity or EPSPS-like activity conferring glyphosate tolerance. An ordinary artisan would have been motivated to have made such a modification in order to have provided a host cell line lacking any background EPSPS activity for the advantage of rapidly detecting novel variants of EPSPS that confer glyphosate tolerance.

11. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Khosla et al in view of Subramanian et al and Sack et al as applied to claims 4, 6-7, 11, 14-16, 18-20, 23-24, 28, 30, 32-33, 35-37, and 61-67, above, and further in view of Aono et al (Plant Cell Physiol. 36(8):1687 [1995]).

While the combined references of Khosla et al, Subramanian et al and Sack et al suggest preparing transgenic plants comprising recombinant herbicide tolerance nucleic acids, the combined references do not teach or suggest breeding such plants "with another plant strain of the same species, and selecting resultant offspring for tolerance to an herbicide." Aono et al disclose that breeding of plants possessing different tolerance genes may be used to prepare plants having multiple mechanisms of herbicide tolerance (see, e.g., p. 1688). Accordingly, in view of the teachings of Aono et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Khosla et al in view of

Subramanian et al and Sack et al so as to have cross fertilized plants possessing different tolerance mechanisms for the advantage of preparing improved crops having multiple mechanisms of tolerance, as suggested by Aono et al.

***Conclusion***

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. It is noted that Sack et al cites Wanke et al (FEBS Lett. 301:271-276 [1992]) as their source of EPT, and that the nucleic acid sequence of Wanke et al is GenBank Accession No. Z11835 (see printout for Accession No. Z11835, Wanke et al, May 1992).

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
March 8, 2002

W. Gary Jones
Supervisory Patent Examiner
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